REMARKS

I. Status Summary

Claims 1-35 were filed with the application. Of these, claims 1-12 and 32-35 have been withdrawn from consideration as being directed to non-elected inventions. Claims 1-12, 18, 21, 22, and 24 have been previously cancelled. Claims 13-17, 19, 20, 23, 25-31 remain pending in the present application. Claims 13-17, 19, 20, 23, and 25-31 presently stand rejected under 35 U.S.C. § 103(a).

The following rejections have been presented in the Final Official Action dated January 14, 2005.

Claims 13-17, 20, and 23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Publication No. 2003/0049620 to Lai *et al.* in view of the journal article to Fulton *et al.* (*Clinical Chemistry*, 43(9):1749-1756 (1997).

Claims 19, 25-28, and 31 presently stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lai *et al.* in view of Fulton *et al.*, as applied to claims 13-17, 20, and 23 of the previous rejection, and further in view of PCT Application No. WO 93/25563 to Wallace et al.

Claims 13-17, and 19 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,639,611 to Wallace et al. in view of the journal article to Gerry *et al.* (*J. Molecular Biology*, 292:251-262 (1999) and further in view of Fulton *et al.*

Claims 20, 23, 25-28, and 31 presently stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the journal article to Chen *et al.* (*Genome Research,* April 2000, 10:549-557) in view of the journal article to Dubiley *et al.* (*Nucleic Acids Research*, 1999, Vol. 23, No. 18, page 19.

Claims 29 and 30 presently stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Chen *et al.* in view of Dubiley *et al.* as applied to claims 20, 23, 25-28, and 31 and further in view of U.S. Patent No. 6,013,431 to Soderlund *et al.*

Claims 29 and 30 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lai *et al.* in view of Fulton *et al.* and the PCT Application to Wallace *et al.*, and further in view of Soderlund *et al.*

Claims 20, 23, 25-31 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,287,778 to Huang *et al.* in view of Fulton *et al.*

An Advisory Action mailed November 3, 2005 (hereinafter "the Advisory Action") was also presented. In the Advisory Action, the Patent Office refused to enter an After Final Amendment B mailed July 14, 2005, upon the contentions that the proposed amendments (a) raise new issues that would require further consideration and/or search; (b) are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and (c) present additional claims without canceling a corresponding number of finally rejected claims.

New claim 36 has been added by the present amendment. Support for the addition of this claim can be found throughout the specification as filed, particularly at paragraph [0061]. Therefore, applicants submit that no new matter has been added by new claim 36.

II. Claim Rejections Under 35 U.S.C. § 103(a)

II.A. Lai et al. in view of Fulton et al.

Claims 13-17, 20, and 23 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Publication No. 2003/0049620 to Lai *et al.* (hereinafter referred to as "Lai *et al.*") in view of the journal article to Fulton *et al.* (*Clinical Chemistry*, 43(9):1749-1756 (1997), hereinafter referred to as "Fulton *et al.*").

The Patent Office asserts that Lai *et al.* teach each element of independent claims 13 and 20, except detection by flow cytometry. The Patent Office contends that Fulton *et al.* teach methods of sorting and detecting microspheres which utilize flow cytometry, and teach these methods in conjunction with nucleic acid hybridization methodologies. The Patent Office asserts that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Lai *et al.* so as to have included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton *et al.*

After careful review of the rejections and the Patent Office's basis therefor, applicants respectfully traverse the rejections and submit the following remarks.

Applicants respectfully submit that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found in either the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re* Fine, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re* Jones, 21 USPQ2d 1941 (Fed. Cir. 1992). Applicants respectfully submit that the combination of references upon which the rejection of the claims relies is improper, in that no suitable suggestion or motivation to combine the references can be found.

As admitted by the Patent Office, Lai *et al.* do not teach or suggest detecting by flow cytometry the hybridization of the extension product to the capture probe by the presence of the detectable label and determining the identify of the single nucleotide polymorphism based on the identity of the microbead. The Patent Office asserts that Fulton *et al.* cures the deficiencies of Lai *et al.* Assuming *arguendo* that Fulton *et al.* teaches the step comprising detection by flow cytometry, applicants submit that there is no valid motivation to combine the references because each teach substantively divergent methods and one of skill in the art would have to engage in considerable experimentation in order to reconcile the two teachings. Even with considerable experimentation, there is no reasonable expectation of success if the two disparate teachings were combined.

Lai *et al.* discloses a detection method wherein microspheres are spectrally encoded through incorporation of semiconductor nanocrystal codes ("SCNCs") in order to incorporate a unique spectral code into a given bead population. Different SCNC populations having the same peak emission wavelength but different peak widths are used to create different codes. Such different populations are mixed to create intermediate linewidths and hence more unique codes. The spectral coding system uses only highly separated spectral peaks having minimal overlap and does not require stringent intensity regulation within the peaks to allow for 100,000 to 10,000,0000 or more unique codes in different schemes.

Fulton *et al.* recites a method wherein microspheres are spectrally encoded through differential dyeing of identically sized microspheres with two different dyes, emitting in two

different wavelengths, permitting discrimination of at least 64 different sets of microspheres. Orange (585nm) and red (>650nm) fluorescence are used for microsphere classification. Unlike Lai *et al.*, which recites creating distinct SCNC microsphere populations having the same peak emission wavelengths, Fulton *et al.* recites a method of creating distinct microsphere populations of unique peak emission wavelengths based on logarithmic orange fluorescence and logarithmic red fluorescence in order to distinguish populations of microspheres. That is, each of the 64 different sets of microspheres will comprise a unique orange/red emission profile. As Lai *et al.* and Fulton *et al.* teach substantively divergent encoding/detection schemes, applicants submit that there is no valid motivation to combine the references and one of skill in the art would have to engage in considerable experimentation in order to reconcile the two teachings.

Applicants further respectfully submit that Fulton *et al.* only recites sweeping statements, such as claims that their system "represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions..." and that their system "...is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis..." offering "excellent sensitivity, precision, speed, and economy" (p. 1775). Applicants respectfully submit that these statements amount to nothing more than an invitation to further investigate, and as such, provide no basis for combining with the disclosure of Lai *et al.*

Thus, the combination of Lai *et al.* in view of Fulton *et al.* does not support the instant rejection of independent claims 13 or 20. Also, claims 14-17 and 23, which depend therefrom are also not rendered obvious by the combination.

In summary, the microspheres recited in Lai *et al.* are not well suited to the method taught by Fulton *et al.* Further, Fulton *et al.* does not contain sufficient teaching as to how to apply the methods therein to the disclosure of Lai *et al.* Hence, applicants contend that a *prima facie* case of obviousness has not been established, and applicants respectfully request the instant rejection of claims 13-17, 20, and 23 be withdrawn.

II.B. Lai et al. in view of Fulton et al. and further in view of Wallace et al.

Claims 19, 25-28, and 31 presently stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lai *et al.* in view of Fulton *et al.*, as applied to claims 13-17, 20, and 23 of the previous rejection, and further in view of PCT Application No. WO 93/25563 to Wallace et al. (hereinafter referred to as "Wallace *et al.*").

The Patent Office concedes that Lai *et al.* in view of Fulton *et al.* does not teach the application of the disclosed methods for diagnosis of a disease, condition, disorder, or predisposition. However, the Patent Office asserts that Wallace *et al.* teach the detection of diseases caused by a defective allele. Thus, the Patent Office contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have utilized the methods taught by Lai *et al.* in view of Fulton *et al.* for the detection of disease as suggested by Wallace *et al.* in order to provide a method for detecting diseases caused by single nucleotide polymorphisms.

After careful review of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

As admitted by the Patent Office, Lai *et al.* do not teach or suggest detecting by flow cytometry the hybridization of the extension product to the capture probe by the presence of the detectable label and determining the identify of the single nucleotide polymorphism based on the identify of the microbead. The Patent Office asserts that Fulton *et al.* cures the deficiencies of Lai *et al.* Applicants respectfully submit that the arguments presented in the above response to the 35 U.S.C. § 103(a) rejection based on Lai *et al.* in view of Fulton *et al.* can further be applied in the instant response. In particular, as addressed above, the microspheres recited in Lai *et al.* are not well suited to the method taught by Fulton *et al.* Further, Fulton *et al.* does not contain sufficient teaching as to how to apply the methods therein to the disclosure of Lai *et al.*

Applicants submit that the disclosure recited in Wallace *et al.* does not cure these deficiencies. Specifically, Wallace *et al.* does not recite a method of detecting by flow cytometry the hybridization of the extension product to the capture probe, as recited in independent claims 13 and 20. Rather, Wallace *et al.* appear to teach attaching a capture

probe to a specific location on a membrane filter, wherein the specificity of the probe is identified by virtue of the location of the probe on the filter. Accordingly, applicants contend that the combination of Lai *et al.* in view of Fulton *et al.*, and further in view of Wallace *et al.*, does not support the instant rejection of claims 13 or 20. Also, claims 19, 25-28, and 31 which depend therefrom are also not rendered obvious by the combination.

Hence, applicants respectfully submit that a *prima facie* case of obviousness has not been established, and applicants respectfully request the instant rejection of claims 19, 25-28, and 31 be withdrawn.

II.C. '611 Patent in view of Gerry et al. and further in view of Fulton et al.

Claims 13-17, and 19 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,639,611 to Wallace et al. (hereinafter referred to as "'611 Patent") in view of the journal article to Gerry *et al.* (*J. Molecular Biology*, 292:251-262 (1999), hereinafter referred to as "Gerry *et al.*") and further in view of Fulton *et al.*

The Patent Office contends that the '611 Patent teaches a method for detecting single nucleotide polymorphisms comprising steps (a)-(c) of the instant application, and the capture of PCR products using a biotin-streptavidin interaction for the detection of a particular allele. The Patent Office concedes that the '611 Patent does not teach a method wherein the forward primer comprises a hybridization tag that identifies the primer, said hybridization tag not complementary to the sequence containing the single nucleotide polymorphism of interest. The Patent Office further concedes that the '611 Patent does not teach hybridizing extension products via the tag to a probe coupled to a particle, detecting the hybridization and identifying the single nucleotide polymorphism based upon the identity of said particle. Further, the Patent Office concedes that '611 Patent does not teach a method wherein at least one primer pair comprises a plurality of primer pairs specific for a plurality of single nucleotide polymorphisms.

The Patent Office asserts that Gerry *et al.* corrects the deficiencies of '611 Patent and that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by the '611 Patent so as to have used the binary primer taught by Gerry *et al.* Specifically, the Patent Office contends

that the use of the ZipCode methodologies taught by Gerry *et al.* with the methods of the '611 Patent would have afforded one of ordinary skill in the art the opportunity to expand the methods taught by the '611 Patent for the detection of multiple mutations and codons.

The Patent Office concedes that the '611 Patent in view of Gerry *et al.* does not teach a method wherein the capture probes are attached to microbeads and wherein the detection occurs by flow cytometry. The Patent Office argues that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by the '611 Patent in view of Gerry *et al.* so as to have provided a microsphere-based assay that included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton *et al.*

After careful review of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

To establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art references when combined. See *In re* Royka 490 F.2d 981, 180 USPQ 580 (CCPA 1974). As conceded by the Patent Office, the '611 Patent does not teach or suggest all the claim limitations of independent claim 13. In particular, the '611 Patent does not teach a forward primer having a hybridization tag that identifies the primer, wherein the hybridization tag is not complementary to the sequence containing the single nucleotide polymorphism of interest. Further, the '611 Patent does not teach a capture probe attached to a microsphere that is specific for the hybridization tag and used to hybridize to the capture probe and identify the single nucleotide polymorphism of interest. The '611 Patent also does not teach detecting by flow cytometry the hybridization of the extension product to the capture probe by the presence of the detectable label.

In contrast, the '611 Patent teaches analyzing the PCR reaction product by gel electrophoresis and visualization of the gel using ethidium bromide staining. Further, the '611 Patent teaches analyzing the PCR product by labeling the product with biotin and capturing the product using streptavidine-agarose. The '611 Patent only teaches analyzing the products on a fixed medium and does not teach or suggest utilizing microbeads in

combination with flow cytometry, which provides several advantages over a solid support medium.

Gerry *et al.* does not provide for the deficiencies of the '611 Patent. Applicants respectfully submit that Gerry *et al.* teaches multiplexed PCR in a single reaction using array-based detection systems. Gerry *et al.* focuses extensively on arrays spotted on polymer surfaces and their advantages over arrays spotted directly on glass surfaces. Gerry *et al.* does not teach or suggest a capture probe coupled to a microbead wherein the microbead identifies the capture probe coupled to a microbead wherein the microbead identifies the capture probe and further detecting by flow cytometry the hybridization of the extension product to the capture probe by the presence of the detectable label.

Applicants further respectfully submit that while Fulton *et al.* disclose specific fluorescently encoded microspheres, Fulton *et al.* recites sweeping statements, such as claims that their system "represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions..." and that their system "...is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis..." offering "excellent sensitivity, precision, speed, and economy" (p. 1775). Therefore, applicants respectfully submit that these statements amount to nothing more than an invitation to further investigate. The disclosure itself does not contain sufficient teaching of how to obtain the desired result when coupled with the disclosures of '611 Patent and Gerry *et al.*

Because all of the features of independent claim 13 are neither taught nor suggested by the '611 Patent, Gerry *et al.* and Fulton *et al.* either alone or in combination, applicants respectfully submit that this combination does not support the instant rejection of independent claim 13. Applicants therefore respectfully request the instant rejection of claim 13 be withdrawn. Since claims 14-17, and 19 directly depend from claim 13, applicants respectfully submit that the cited combination does not support the instant rejection of these claims. As such, applicants request the instant rejection of claims 13-17 and 19 be withdrawn at this time.

II.D. Chen et al. in view of Dubiley et al.

Claims 20, 23, 25-28, and 31 presently stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the journal article to Chen *et al.* (*Genome Research,* April 2000, 10:549-557, hereinafter referred to as "Chen *et al.*") in view of the journal article to Dubiley *et al.* (*Nucleic Acids Research*, 1999, Vol. 23, No. 18, page 19, hereinafter referred to as "Dubiley *et al.*").

The Patent Office contends that Chen *et al.* teach each step of independent claim 20. However, the Patent Office concedes that Chen *et al.* do not teach a method wherein at least one primer comprises a group of at least 2 primers, each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest.

The Patent Office asserts that Dubiley *et al.* meets the deficiencies of Chen *et al.* and teach a single nucleotide extension method for the detection of polymorphic alleles which utilize primers that contain different 3'-terminal nucleotide overlapping the variable DNA, and teach a group of at least 2 primers having a 3' end specific for different alleles of a single nucleotide polymorphism of interest.

The Patent Office further asserts that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have utilized the primers taught by Dubiley *et al.* in the methods taught by Chen *et al.* so as to have provided a method which utilizes a pair of at least 2 primers, each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest. The Patent Office contends that the use of such primers would have provided an alternate methodology for the detection of single nucleotide polymorphisms using the basic methodology taught by Chen *et al.*, as Dubiley *et al.* teach that the use of primers that end adjacent to or overlap with the polymorphic site have comparable specificity with regard to one other.

After careful review of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

As noted above, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references

themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim elements. MPEP 2142; *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Patent Office asserts that the primers taught by Dubiley *et al.* can be utilized in the methods taught by Chen *et al.* to meet the limitations of independent claim 20. Applicants respectfully submit that there is no motivation or suggestion in the art to combine the reference teachings.

Applicants respectfully submit that Dubiley *et al.* disclose primers that have been immobilized to a gel pad of a microchip. Hybridization of DNA with the immobilized primer occurs by contacting the primer with the target DNA, and primer extension occurs in the presence of the microchip, as the primers remain attached. Chen *et al.*, on the other hand, disclose a method whereby a mobilized primer is contacted with the target DNA, SBCE reaction carried out with labeled nucleotides, and the primer is then hybridized to a microbead by the ZipCode sequence of the primer.

Further, applicants respectfully submit that the primer disclosed in Chen *et al.* contains a unique ZipCode sequence that is used to allow the SBCE product to be hybridized to the appropriate microsphere for detection by flow cytometry. That is, the ZipCode at the 5'-end of the primer allows the resulting enzymatic reaction product to be captured by its complementary sequence, which has been coupled to a specific fluorescent microsphere. The primers recited in Dubiley *et al.* do not comprise such a unique sequence used to attach the primer to the gel pad. Each primer is attached in an identical way, whereby the primer is immobilized through reductive coupling of the 5'amino group of the primer with the aldehyde group of the activated gel pad. Unlike Chen *et al.*, the primers do not contain a distinct ZipCode sequence, and thus the primers recited in Dubiley *et al.* would not allow coupling to its specific fluorescent microbead.

Thus, applicants respectfully submit that there is no suggestion or motivation in the references themselves to modify the reference or to combine the reference teachings

because the primers recited in Dubiley *et al.* are functionally different than the primers recited in the method taught in Chen *et al.* Further, applicants respectfully submit that if the primers recited in Dubiley *et al.* were combined with the method taught by Chen *et al.*, undue experimentation would be required to modify either the method of Chen *et al.* or the primers of Dubiley *et al.* to provide the claimed method, as the Dubiley *et al.* recited primers are immobilized and do not comprise a unique ZipCode sequence to attach each primer to its corresponding fluorescent microbead. As such, the combination of Chen *et al.* and Dubiley *et al.* do not teach a method wherein at least one primer comprises a group of at least 2 primers, each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest, as recited in independent claim 20.

Hence, applicants respectfully submit that a *prima facie* case of obviousness has not been established as to independent claim 20. Therefore, as claims 23, 25-28, and 31 depend directly from independent claim 20, a *prima facie* case of obviousness has not been established as to these claims as well. As such, applicants respectfully request the instant rejection of claims 20, 23, 25-28, and 31 be withdrawn at this time.

II.E. Chen et al. in view of Dubiley et al. and further in view of Söderlund et al.

Claims 29 and 30 presently stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Chen *et al.* in view of Dubiley *et al.* as applied to claims 20, 23, 25-28, and 31 and further in view of U.S. Patent No. 6,013,431 to Söderlund *et al.* (hereinafter referred to as "Söderlund *et al.*").

The Patent Office asserts that the teachings of Chen *et al.* in view of Dubiley *et al.* are applied to claims 29 and 30 as they are applied in the rejection of claims 20, 23, 25-28, and 31. The Patent Office concedes that while Chen *et al.* utilize labeled chain terminating nucleoside triphosphates, Chen *et al.* do not teach a method wherein a plurality of chain-terminating nucleoside triphosphates, each comprising a unique label are used, as is recited in claims 29 and 30.

The Patent Office contends that Söderlund *et al.* teach single nucleotide primer extension methods wherein a plurality of chain-terminating nucleoside triphosphates, each

comprising a unique label, are used for the detection of more than one point mutation occurring at the same site of one undivided sample.

The Patent Office asserts that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method taught by Chen *et al.* so as to have included differentially labeled ddNTPs as taught by Söderlund *et al.* within the reaction mixture in order to detect more than one point mutation occurring at the same site of an undivided sample.

After careful review of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

Applicants respectfully submit that the arguments presented in the above response to the 35 U.S.C. § 103(a) rejection of independent claim 20 based on Chen *et al.* in view of Dubiley *et al.* can further be applied in the instant response. In particular, as addressed above, applicants submit that there is no suggestion or motivation in the references themselves to modify the reference or to combine the reference teachings because the primers recited in Dubiley *et al.* are functionally different than the primers recited in the method taught by Chen *et al.* Further, applicants respectfully submit that if the primers recited in Dubiley *et al.* were combined with the method taught by Chen *et al.*, undue experimentation would be required to modify either the method of Chen *et al.* or the primers of Dubiley *et al.*, as the Dubiley *et al.* primers as recited are immobilized and do not comprise a unique ZipCode sequence to attach each primer to its corresponding fluorescent microbead.

Applicants submit that Söderlund *et al.* does not cure the above-noted deficiencies. Söderlund *et al.* teaches the use of at least one primer complementary to the nucleotide sequence 3' from the variable nucleotide to be detected, and detecting a labeled NTP incorporated by extension of the detection step primer. The primers recited in Söderlund *et al.* do not provide a hybridization tag, as taught in the method of Chen *et al.*

Therefore, applicants respectfully submit that there is no suggestion or motivation in the references themselves to modify the references or to combine the reference teachings because the primers recited in Dubiley *et al.* and Söderlund *et al.* are functionally different

than the primers recited in the method taught in Chen *et al.* Further, applicants respectfully submit that if the primers recited in Dubiley *et al.* or Söderlund *et al.* were combined with the method taught by Chen, undue experimentation would be required to modify either the method of Chen *et al.* or the primers of Dubiley *et al.* or Söderlund *et al.*, as the Dubiley *et al.* primers as recited are immobilized and neither the Dubiley *et al.* primers not the Söderlund *et al.* primers comprise a unique ZipCode sequence to attach each primer to its corresponding fluorescent microsphere.

Therefore, the combination of Chen *et al.* in view of Dubiley *et al.* and further in view of Söderlund *et al.* does not recite a method wherein at least one primer comprises a group of at least 2 primers, each primer in said group having a 3' end specific for a different allele of a single nucleotide polymorphism of interest, as recited in independent claim 20. Therefore, applicants contend that a *prima facie* case of obviousness has not been established as to independent claim 20. Since claims 29-30 depend directly from independent claim 20, applicants respectfully submit that a *prima facie* case of obviousness has not been established as to these claims as well. As such, applicants respectfully request the instant rejection of claims 29 and 30 be withdrawn at this time.

II.F. Lai et al. in view of Fulton et al. and Wallace et al., and further in view of Söderlund et al.

Claims 29 and 30 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lai *et al.* in view of Fulton *et al.* and Wallace *et al.*, and further in view of Söderlund *et al.*

The Patent Office asserts that the teachings of Lai *et al.* in view of Fulton *et al.* and Wallace *et al.* are applied to claims 29 and 30 as they were previously applied to claims 19, 25-28, and 31. The Patent Office contends that while Wallace *et al.* teach methods which utilize labeled chain terminating nucleoside triphosphates, Wallace *et al.* do not teach a method wherein a plurality of chain-terminating nucleoside triphosphates, each comprising a unique label are used, as is recited in claims 29 and 30.

The Patent Office asserts that Söderlund *et al.* teach single nucleotide primer extension methods wherein a plurality of chain-terminating nucleoside triphosphates, each

comprising a unique label are used for the detection of more than one point mutation occurring at the same site out of one undivided sample.

The Patent Office argues that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method taught by Lai *et al.* in view of Fulton *et al.* and Wallace *et al.* so as to have included differentially labeled ddNTPs as taught by Söderlund *et al.* within the reaction mixture in order to detect more than one point mutation occurring at the same site of an undivided sample.

After careful review of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

As admitted by the Patent Office, Lai *et al.* do not teach or suggest detecting by flow cytometry the hybridization of the extension product to the capture probe by the presence of the detectable label and determining the identify to the single nucleotide polymorphism based on the identify of the microbead. The Patent Office asserts that Fulton *et al.* cures the deficiencies of Lai *et al.* Applicants respectfully submit that the arguments presented in the above response to the 35 U.S.C. § 103(a) rejection based on Lai *et al.* in view of Fulton *et al.* can further be applied in the instant response. In particular, as addressed above, the microspheres recited in Lai *et al.* are not well suited to the method taught by Fulton *et al.* Further, Fulton *et al.* does not contain sufficient teaching as to how to apply the methods therein to the disclosure of Lai *et al.*

Applicants submit that the disclosure recited in Wallace *et al.* does not cure the deficiencies. Specifically, Wallace *et al.* does not recite a method of detecting by flow cytometry the hybridization of the extension product to the capture probe, as recited in independent claims 13 and 20. Rather, Wallace *et al.* teach attaching a capture probe to a specific location on a membrane filter, wherein the specificity of the probe is identified by virtue of the location of the probe on the filter.

Applicants further submit that the disclosure recited in Söderlund *et al.* does not cure these deficiencies. Specifically, Söderlund *et al.* does not recite a method of detecting

by flow cytometry the hybridization of the extension product to the capture probe, as recited in independent claims 13 and 20.

Therefore, applicants respectfully submit that the combination of Lai *et al.* in view of Fulton *et al.* and Wallace *et al.*, and further in view of Söderlund et al. does not support the instant rejection of independent claim 20. Also, claims 29 and 30, which depend therefrom are also not rendered obvious by the combination.

Hence, applicants contend that a *prima facie* case of obviousness has not been established, and applicants respectfully request the instant rejection be withdrawn.

II.G. Huang et al. in view of Fulton et al.

Claims 20, 23, 25-31 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,287,778 to Huang *et al.* (hereafter referred to as "Huang *et al.*") in view of Fulton *et al.*

The Patent Office contends that Huang *et al.* teach a method comprising each step of independent claim 20 except a method wherein the detection is by flow cytometry.

The Patent Office asserts that Fulton *et al.* teach methods of sorting and detecting microspheres which utilize flow cytometry, and in particular teach these methods in conjunction with nucleic acid hybridization methodologies.

The Patent Office argues that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Huang *et al.* so as to have included a flow cytometry step for the detection of hybridization of the extension product, as taught by Fulton *et al.* The Patent Office asserts that one would have been motivated to use flow cytometry to detect the microspheres taught by Huang *et al.* in order to take advantage of such a system as taught by Fulton *et al.*

After careful review of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

As noted above, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to

modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim elements. MPEP 2142; *In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully submit that there is no motivation or suggestion to combine the references. Huang *et al.* recites a method wherein a region of DNA is amplified, allele-specific extension primers are labeled, and hybridization of the products to an array of probes occurs whereby a genotype is identified from the pattern of hybridization. From the disclosure of Huang *et al.* (col. 5, lines 44-47), the extension product can be hybridized to one or more probes which are immobilized to known locations on a solid support, e.g., in an array, microarray, high density array, beads or microtiter dish. Applicants submit that Huang *et al.* appears to recite that the extension products are hybridized to probes immobilized to a known location on a solid support. In Fulton *et al.*, each type of hybridization tag is not immobilized to a known location on a fluorescently labeled microsphere; rather, each microsphere contains one type of hybridization tag and the microbead is uniquely labeled by a specific red/orange emission profile in order to determine which specific hybridization tag corresponds to each microsphere.

As such, applicants submit that the beads to which the labeled extension product can bind as recited by Huang *et al.* are substantially divergent from the fluorescently labeled microbeads recited in Fulton *et al.* The microbeads taught by Fulton *et al.* are fluorescently labeled with a unique red/orange emission profile and each microsphere class contains a distinct hybridization tag that binds a tag corresponding to a unique labeled extension product. The beads recited in Huang *et al.* are not fluorescently labeled and the hybridized nucleic acids are detected by detecting the labels attached to the target nucleic acids and noting the location of the detected extension product on the solid support, not by detecting both the labeled product and the labeled microbead.

Further, applicants respectfully submit that Fulton *et al.* recites sweeping statements, such as claims that their system "represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular

interactions..." and that their system "...is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis..." offering "excellent sensitivity, precision, speed, and economy" (p. 1775). Applicants respectfully submit that these statements amount to nothing more than an invitation to further investigate. The disclosure itself does not contain sufficient teaching of how to obtain the desired result when applied to the teachings of Huang *et al.* Therefore, applicants respectfully submit that the combination of Huang *et al.* in view of Fulton *et al.* does not support the instant rejection of independent claim 20. Also, claims 23, and 25-31, which depend therefrom, are also not rendered obvious by the combination.

As such, applicants respectfully submit that there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings such that independent claim 20 is rendered obvious. Accordingly, applicants respectfully submit that the combination of Huang *et al.* in view of Fulton *et al.* does not support the obviousness rejection of claim 20, or claims 23, and 25-31 which depend from claim 20.

Hence, applicants contend that a *prima facie* case of obviousness has not been established, and applicants respectfully request the instant rejection of claims 20, 23, and 25-31 be withdrawn.

III. New Claim

New claim 36 has been added by this amendment as indicated above. Support for this claim can be found throughout the specification as filed, particularly at paragraph [0061]. Therefore, applicants respectfully submit that no new matter has been added by new claim 36.

New claim 36 recites a method of detecting a single nucleotide polymorphism comprising the steps of claim 13, except that the reverse primer comprises the hybridization tag that identifies the primer, instead of the forward primer, as recited in claim 13.

None of the prior art references cited in the instant rejection recite a method of

detecting a single nucleotide polymorphism wherein the reverse primer comprises the hybridization tag that identifies the primer.

Therefore, claim 36 is believed to be patentably distinguished over the cited art of record and allowance of this claim is therefore respectfully requested.

CONCLUSIONS

In light of the above Remarks, it is respectfully submitted that the present application is now in a proper condition for allowance and such action is earnestly solicited. If any minor issues should remain outstanding after the Patent Examiner has had an opportunity to study the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney so that all such matters may be resolved and the application be placed in a condition for allowance without the necessity for issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this Amendment to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON & TAYLOR, P.A.

Date: 11/14/2005 By: _____

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